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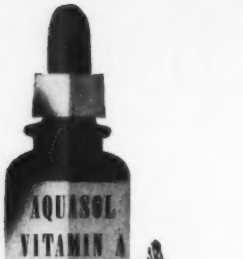

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CHLOROAMPHENICOL* IN THE TREATMENT OF PRIMARY ATYPICAL PNEUMONIA

Case Report No. 170

Adrian Recinos, Jr., M.D.
Bennett Olshaker, M.D.
Sidney Ross, M.D.

Until recently the treatment of primary atypical pneumonia has been disappointing. The sulfonamides and penicillin, though highly effective against bacterial pneumonia, have produced no benefit in the atypical type. Indeed, the failure of a patient with pneumonia to respond to these agents constitutes one of the criteria for the diagnosis of primary atypical pneumonia. Within the past year a new antibiotic, aureomycin, has been shown by several investigators[1, 2, 3] to be effective in a number of patients with primary atypical pneumonia. Although the success of chloroamphenicol in this disease has not been established, its similarity to aureomycin in its in vitro and in vivo range of activity,[4] particularly against the rickettsiae and certain viral agents, would seem to justify its trial in the treatment of primary atypical pneumonia.

Chloroamphenicol is an antibiotic derived from a strain of Streptomyces venezualae. It has a wide range of antimicrobial activity which includes gram positive and gram negative bacteria, the rickettsiae, and the viral agents of the psittacosis-lymphogranuloma group.[5] Effective serum levels of the drug are readily obtained by its oral administration, a route attended by no known toxic manifestations.

Chloroamphenicol has been recommended in the treatment of atypical pneumonia.[6] However, at this writing no series of cases or individual case reports have appeared to confirm its value in this disease. Woodward,[4] in a recent monograph on aureomycin and chloroamphenicol, cites a patient who was benefited by the latter drug, but does not give a detailed report.

The following case report serves to illustrate the apparently beneficial effect exerted by chloroamphenicol in a patient with primary atypical pneumonia.

Case Report W. S. 49–3517

W. S., a twenty-three years old graduate nurse, was admitted to the hospital with a history of headache, generalized aching, fever, malaise,

* Chloromycetin—Parke-Davis. Chloromycetin supplied by the Parke-Davis Company.

chilly sensations and a slightly productive cough. All these symptoms were of thirty-six hours duration. On the day before admission she had received 300,000 units of procaine penicillin intramuscularly without apparent benefit.

The past history and family history were not contributory to the present illness.

On admission the patient appeared acutely ill and drowsy. She had a temperature of 104°F., a pulse of 110, and respiratory rate of 25 per minute. There was no dyspnea. Examination of the chest revealed dullness to percussion, bronchial breathing, and numerous fine moist râles over the right base posteriorly. There were no other positive physical findings. X-ray of the chest disclosed an opacity over the entire lower right lobe having the appearance of a lobar pneumonia.

The leukocyte count was 16,800 with 87 per cent neutrophiles. Urinanalysis was normal. A blood culture was sterile and sputum culture yielded a poor growth of pneumococcus (too few to type) and pseudomonas aeruginosa. Cold hemagglutinins on the day of admission were present in a titer of 1:32 and the streptococcus MG agglutinin titer was negative.

A tentative diagnosis of pneumococcal lobar pneumonia was made and the patient started on penicillin (50,000 units every three hours) intramuscularly and sulfadiazine (3 grams initially and then 1 gram every four hours) by mouth.

For the first four hospital days, except for a drop in the white count from 16,800 to 6,000, there was no appreciable change in the patient's condition. She maintained an elevated temperature in the neighborhood of 101°F. to 102°F. On the fourth day blood and sputum cultures were repeated with similar results as on admission. An atypical pneumonia was suspected and at this time chloroamphenicol therapy was instituted. One-half gram of the drug was given every three hours for ten doses and then every six hours for nineteen doses. Within twenty-four hours after chloroamphenicol was started the patient was afebrile and symptomatically improved. Sulfadiazine was discontinued twenty-four hours after chloroamphenicol was initiated and penicillin after forty-eight hours.

The patient remained free of symptoms and afebrile throughout the remainder of her hospital stay. Chest findings on physical examination cleared slowly but there was no change in the density seen by x-ray.

Pneumococci were isolated from the sputum on the eighth day and beta hemolytic streptococci on the twelfth. The cold hemagglutinin titer had risen to 1:512 on the twelfth day, but the Streptococcus MG agglutinin titer was still negative. The patient was discharged in good condition on the sixteenth hospital day.

She remained well at home and returned for a follow-up visit four weeks

later. X-rays showed the persistent consolidation to have cleared completely. At this time, five weeks after the onset of her illness, the cold hemagglutinin titer had risen to 1:2048 and the Streptococcus MG agglutination was positive in a dilution of 1:40.

The final diagnosis was primary atypical pneumonia.

The patient's course in the hospital is illustrated in figure 1.

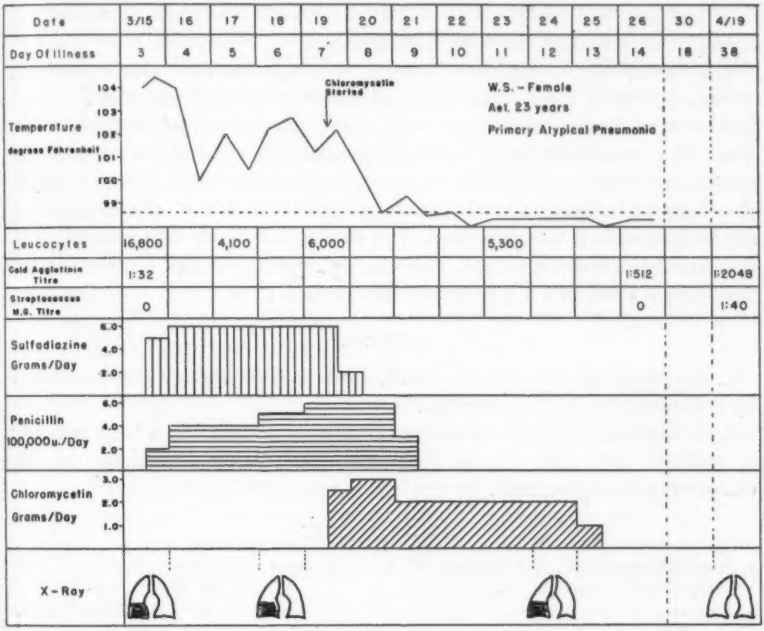

FIG. 1. W. S.

DISCUSSION

The clinical pattern in this patient satisfies the criteria for the diagnosis of primary atypical pneumonia. Symptoms of headache, malaise, chilly sensations, and non-productive cough were present and are commonly described in this disease. Pulmonary consolidation and leukocytosis, while not the rule, are found in a small proportion of cases. The lack of appreciable numbers of bacterial pathogens in the sputum and the failure of sulfadiazine and penicillin to alter the course of the disease favor the diagnosis of primary atypical pneumonia. The most convincing evidence, however, lies in the serological studies. A rising titer of cold hemagglutinins

and agglutinins for Streptococcus MG, as demonstrated in this patient's serum during the course of her illness and convalescence, is highly significant in establishing the diagnosis of primary atypical pneumonia. Horsfall[7] has reported that in at least one-half of cases of atypical pneumonia, the cold hemagglutinins appear in a significant titer of 1:40 or above within two to four weeks after the onset of illness while the Streptococcus MG agglutinins in titers of 1:20 or above, appear from three to five weeks. Our case followed this pattern with the Streptococcus MG agglutinins lagging in appearance behind the cold hemagglutinins.

Chloroamphenicol appeared to exert a prompt and favorable response in this patient's illness. Her temperature was normal and she felt and looked much improved within twenty-four hours after the drug was initiated. She remained afebrile and comfortable and except for a delay in resolution of the consolidation by x-ray, her convalescence was uneventful. The drug was employed in an early stage (the seventh day) of a moderately severe illness. It is unlikely, then, that this prompt favorable response was the product of a spontaneous remission although the extreme variability of this disease precludes a more positive statement.

SUMMARY

1. A case of primary atypical pneumonia apparently favorably affected by chloroamphenicol is presented.

2. A thorough clinical evaluation of chloroamphenicol in a large number of patients were virus pneumonia is necessary before its efficacy in this disease can be determined.

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CHRONIC LEAD POISONING ASSOCIATED WITH EOSINOPHILIA AND SPLENOMEGALY

Case Report No. 171

John P. McGovern, M.D.
Eileen Simmons, M.D.

E. G. 49–9294

E. G., a two and three-fourths year old white female was first admitted to Children's Hospital on August 1, 1949 with a chief complaint of vomiting of eight days' duration. The present illness was ushered in with rather severe vomiting, the child being able to retain nothing by mouth. Other than the persistent vomiting, there were no symptoms in evidence until the following day when she passed three soft, foul smelling, green stools without blood or mucous. At this time the patient was taken to a physician who prescribed "some capsules" which apparently proved ineffective, as the diarrhea and vomiting continued. The child was first seen in the Out-Patient Department of this hospital five days after the onset of symptoms or three days before the first hospital admission. There were no objective findings at this time and treatment consisted of general measures for non-specific gastro-enteritis.

The patient returned to the Out-Patient Department two days later, the diarrhea having been controlled. The following day because of recurrence of severe vomiting associated with coughing the child was brought to the hospital and was admitted for further study.

The family history was essentially non-contributory, there being no history of asthma, hay fever, eczema or other allergic manifestations. In the past history, however, it was noted that since the age of six months, the child had had numerous recurrent episodes of vomiting which the parents associated with "riding in the automobile."

Physical examination on admission revealed a pale, malnourished, moderately dehydrated child appearing chronically ill. The pharynx was hyperemic. The spleen which was firm and not tender could be palpated 5 to 6 cm. below the left costal margin. The remainder of the examination was within usual limits.

The accessory clinical findings on admission revealed: serological tests for syphilis and tuberculin test to be negative; a hemogram of 10.5 grams hemoglobin; 4.5 million red cells; 7,600 white cells with a differential count of 50 per cent polymorphonuclear leukocytes, 43 per cent lymphocytes, and 7 per cent eosinophiles; a normal platelet count; a negative heterophile agglutination test; and stool examination for ova and parasites was negative.

Following adequate hydration with parenteral fluids, vomiting ceased. The hemoglobin at this time was 8 grams. Two transfusions of 300 ml. of whole blood each were given which increased the hemoglobin to 14.5 grams.

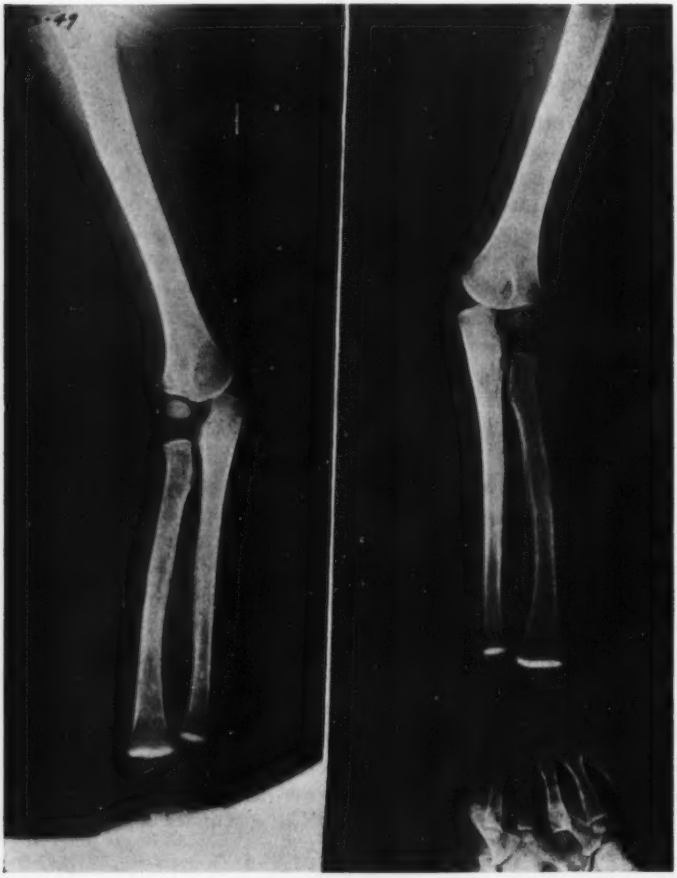

FIG. 1

FIGS. 1 and 2. E. G. Heavy metal deposits which are quite clearly seen at the ends of the long bones.

The spleen remained enlarged throughout the hospital stay; the eosinophilia reached a maximum of 15 per cent.

The child was discharged on the twelfth hospital day with the etiology of the splenomegaly, eosinophilia and anemia remaining unexplained.

On the following day, information was obtained that the four year old brother of this patient had died suddenly of lead intoxication, proven by post-mortem examination. In view of this fact, the patient was readmitted for further studies.

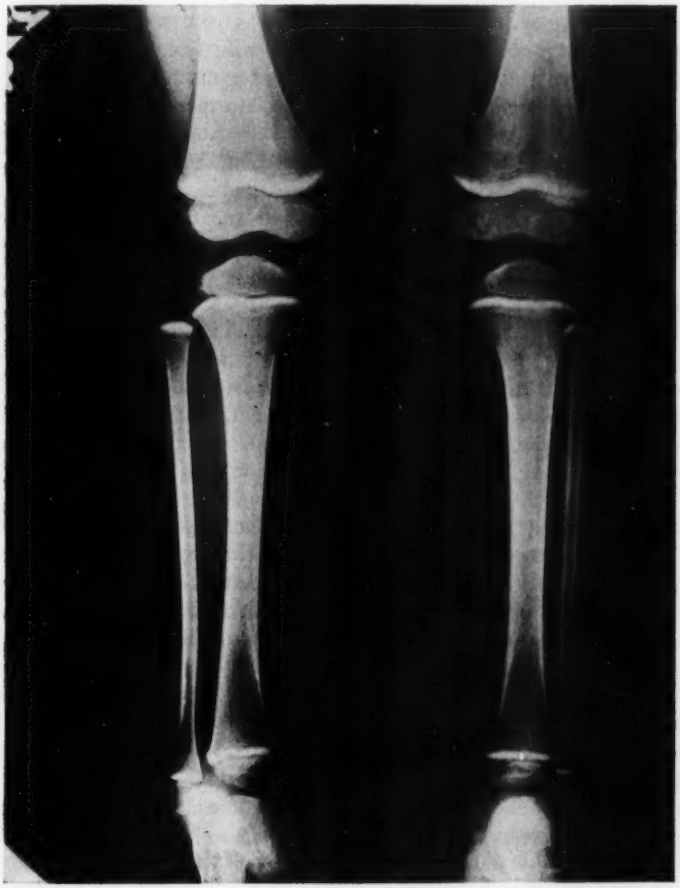

FIG. 2

Additional history obtained at this time revealed that the child had been known to chew on numerous household articles, including repainted chairs and tables. We were unable to obtain reliable or detailed information as to exactly how long the habit had been observed, or how frequently the child had ingested paint.

Physical findings were essentially the same as on the previous admission. Examination of the blood on repeated occasions revealed normal hemoglobin levels together with normal red cell and platelet counts. The eosinophilia persisted ranging from 9 per cent to 20 per cent. Repeated examination of the red cells with special staining techniques showed no evidence of basophillic stippling. Examination of the stools for ova and parasites was negative on three occasions. The trichinellin skin test was also negative. Quantitative determination of lead concentration in the blood on admission revealed 0.070 mgm./100 grams of blood while the excretion of lead was found to be 0.34 mgm./100 ml. of urine. A cutaneous zinc sulfide test for lead in the tissues was positive.[1] X-ray examination of the long bones in the upper and lower extremities revealed marked dense lines at the metaphyses, characteristic of lead poisoning. (See Figs. 1 and 2.)

Therapy during the second hospital admission consisted of 30 drops of viosteril with 6 grams of sodium citrate daily, a modification of the method used by Ketz and Litroff.[2]

The course in the hospital was uneventful and at the time of discharge on the twenty-fourth hospital day examination of the long bones of the upper and lower extremities revealed little change since admission examination. Blood concentration of lead was 0.080 mgm./100 grams of blood with a urinary lead concentration of 0.010 mgm./100 ml. of urine.

DISCUSSION

From the history of paint ingestion, the increased blood and urinary lead levels, the positive zinc sulfide test and the highly suggestive x-ray evidence in the long bones, we can conclude that this patient had chronic lead absorption. That the symptomatology anemia, eosinophilia and splenomegaly were all due to the chronic ingestion of lead cannot be stated categorically, for nowhere in the literature were we able to find eosinophilia and splenomegaly associated with plumbism. In consideration of these facts, it was felt that a report of this case would be of value for the following reasons: (1) to emphasize the point that chronic painless vomiting associated with anemia is one of the most common early symptoms of plumbism in children; (2) that because of the protean manifestations of lead poisoning numerous cases are probably left undiagnosed, as was illustrated by the first admission of this child to the hospital; and (3) to document the possibility that with the findings of unexplained splenomegaly and eosinophilia we may be dealing with a new or heretofore unobserved symptom-complex of plumbism.

The presence of symptoms in any given case of chronic lead exposure is dependent on many factors. In addition to the length, rate, and degree of absorption, the amount of lead in active transport is related to metabolic

factors, such as acidosis and defects of nutrition, including low calcium diet which may initiate symptoms.[3] The content of lead in the urine roughly parallels the lead concentration in the blood and they both are an indication of the rate of transport but not necessarily an accurate estimate of the degree of toxicity. According to Kehoe[4] the urine of normal individuals with no lead exposure may be as high as 0.002 mgm./100 ml. of urine. He found that most cases of lead poisoning examined during periods of clinical toxicity showed concentrations between 0.01 and 0.02 mgm./100 ml. of urine. The urinary concentration of lead in our patient on admission was 0.034 mgm./100 ml. He further stated that although the amount may reach 0.011 to 0.012 mgm./100 ml. without clinical signs of toxicity, in his experience when the concentration exceeded the latter value, symptoms of lead intoxication would be present. Normal blood lead values were placed at 0.005 to 0.05 mgm./100 grams of blood; whereas findings in excess of 0.07 mgm. were indicative of lead exposure within some recent period. The levels in our case were 0.07 mgm. and 0.08 mgm./100 grams of blood. Symptoms of toxicity may not be present at this level but are likely to occur if exposure is chronic or intensified by metabolic disorders.

The helpful diagnostic aids of basophilic stippling of the red blood cells and the presence of lead line in the gums were not present in this case. This, however, is not too unusual for a lead line is present only when oral hygiene is poor and lead poisoning may exist without basophilic stippling. The degree of stippling when present does not correlate with the magnitude of exposure or symptomatology. At times stippled cells may be found in non-exposed normal persons in numbers up to 7,000 per one million erythrocytes.[5] The severe abdominal colic, constipation and neuritis so classically found in adults is less frequently seen in children, whereas painless vomiting (rare in adults) is perhaps the earliest and often the only symptom of chronic lead poisoning in children.[6] Diarrhea is on record but is not commonly associated with plumbism.

The etiology of the eosinophilia and splenomegaly in this case remains an enigma unless one can associate it with the syndrome of lead intoxication. The possibility of a dual disease process was entertained but none of the causes of combined eosinophilia and splenomegaly could be demonstrated. A review of the literature was made to ascertain whether or not splenomegaly or eosinophilia has been associated with acute or chronic lead poisoning. Rather thorough studies had been made of the complete hematological picture in plumbism yet no reference to changes in the eosinophiles could be found. Significant changes in any of the leukocytes as well as the platelets do not occur except in severe acute intoxication and these cell changes occur in the lymphocytic series.[5] Absorption of lead causes an increase in the ratio of large lymphocytes plus monocytes to small lymphocytes.

According to Shields,[7] the magnitude of this ratio is more closely associated with clinical toxicity than is the stippled cell count.

Since lead storage may take place in various organs of the body it is possible that excess deposits in the spleen could conceiveably cause chronic pathological changes in that organ with subsequent enlargement. However, this possibility does not seem to be substantiated by the survey of the literature. Lead that reaches the systemic circulation is deposited in the bone and soft tissues particularly the liver, kidney, pancreas, and brain. Intranuclear inclusion bodies are sometimes found in the pancreas, liver, and kidneys, probably indicating specific cellular damage.[3] According to Artz,[1] necropsy reveals an increase in lead found in liver, kidneys, and spleen. In a review of seventy-five autopsies,[8] the amount of lead in various organs listed in order of frequency were bone, liver, and kidney. That splenomegaly could be the result of a generalized toxic reaction, apart from the storage of lead in the organ, must be considered.

SUMMARY

1. A case of chronic lead poisoning associated with eosinophilia and splenomegaly is presented.

2. A survey of the literature failed to reveal a single case of plumbism with associated eosinophilia and splenomegaly.

3. No separate disease process could be demonstrated as the etiology of the eosinophilia and splenomegaly.

4. It is concluded from these findings that one must strongly consider the probability that this case represents a new symptom-complex, that of plumbism with eosinophilia and splenomegaly.

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HEMOLYTIC MACROCYTIC ANEMIA

Case Report No. 172

Hassan Ahari, M.D. C. B. 49-3032

C. B., a one year old white boy, was admitted to The Children's Hospital as a private patient of Dr. P. A. McLendon on March 4, 1949 with a tentative diagnosis of leukemia.

The history revealed that the infant was apparently well until twelve days prior to admission when he began to have intermittent diarrhea which varied in intensity during the following seven days. He had been successfully vaccinated against smallpox before the diarrhea began and the scab from the vaccination was still present. Three days prior to admission, the infant's mother noted his color was poor and that his skin appeared "waxen." His appetite became poor and he was breathing rapidly. The parent described a rapid change in the infant's general health within a few days. After examination by the family physician, a blood count showed a picture which a hematologist thought suggestive of leukemia. Further study and hospitalization was advised.

Past history revealed that the infant was born in Columbia Hospital at term, following an uneventful pregnancy. The birth weight was 3540 grams (seven pounds, six ounces).

Feeding consisted of evaporated milk formula and vitamin drops. Routine immunizations for diphtheria, pertussis, and tetanus had been given. In regard to growth and development, the mother stated that the infant seemed to be somewhat slow. The only previous ailment was bronchitis at the age of five weeks which cleared up with appropriate treatment.

The family history was negative except that the father had hay fever. There was a three and one-half year old girl sibling in good health.

Physical examination on admission showed a well developed and well nourished white male infant who appeared pale, irritable, and ill. The temperature was 101.2 F., pulse 158, and respirations 28. The frontal bosses were somewhat protruded. The skin and conjunctival mucous membranes were quite pale. The remainder of the physical examination was negative. No lymphadenopathy or splenomegaly was observed. Initial laboratory data revealed hemoglobin 7 grams; erythrocytes 2,700,000 with 1,700 nucleated red blood cells; leukocytes 32,500 with 34 per cent neutrophiles, 9 per cent lymphocytes, and 48 per cent atypical cells, possibly lymphocytes or erythroblasts. Thrombocyte count was 75,000 per cubic millimeter. The bleeding and coagulation time were within normal limits. Bone marrow puncture was performed on March 5, erythroid hyperplasia of the megaloblastic type being reported.

Other initial laboratory examinations included: a negative blood culture and Wassermann, reticulocyte count which was 10 per cent, icterus index 15 units, van den Bergh test: qualitative delayed direct, quantitative 1.15 mgm. bilirubin per 100 cc. of blood. A fragility test was within normal limits. The urinalysis on the fifth hospital day showed a moderate amount of albumin and many red blood cells and white blood cells.

The infant was started on Crystacillin 300,000 units twice daily and 15 units of liver extract intramuscularly daily. Transfusion of 200 cc. of whole blood was given on five occasions. The temperature curve ranged from 97.4 F. to 102.4 F.

The patient responded very well to treatment. Daily hemogram showed a gradual increase of the hemoglobin, erythrocytes, and thrombocytes coincident with a decrease in leukocytes and reticulocytes. Laboratory data on the day of discharge March 15 (eleventh hospital day), revealed hemoglobin 12.5 grams; erythrocytes 3,700,000; leukocytes 7,100 with 30 per cent neutrophiles and 60 per cent lymphocytes; thrombocytes 350,000 per cubic millimeter; reticulocytes 2 per cent; icterus index and van den Bergh tests were within normal limits. Urinalysis was similar to that of the previous examination.

The infant has been doing well since and several subsequent blood studies have been reported as normal.

DISCUSSION

E. Clarence Rice, M.D.: The report states that the patient rather suddenly became anemic, his blood showing reticulocytosis, the presence of nucleated red blood cells, microcytes, macrocytes, and spherocytes, plus an excess of bilirubin. The bone marrow exhibited erythroid hyperplasia and megaloblastosis. Hematuria was present. A satisfactory collection of feces was not obtained for urobilinogen determination. No iso-hemolysins were present and increased fragility was not demonstrated. No hereditary factor was found. Syphilis could apparently be excluded but other infection seemed possible. The diarrhea or small pox vaccination may have been responsible for the illness. One blood culture failed to produce a growth.

Wintrobe lists the following as causes of acute and subacute hemolytic anemia:

1. Protozoal parasites
2. Bacterial toxins
3. Chemical agents
4. Vegetable poisons
5. Animal poisons
6. Naturally occurring agglutinins alpha and beta (mismatched transfusions)

7. Hemolysins of the immune-body type
   a. Paroxysmal hemaglobinuria e frigore
   b. Acute acquired anemia of unknown etiology ("hemolysinic" icterus, "Lederer's anemia")
8. Acute hemolytic anemia of unknown etiology without demonstrable hemolysins ("Lederer's anemia")
9. Acute exacerbation of chronic hemolytic anemia

The patient's anemia would seem to be due either to the effect of bacterial toxins or possibly it may be representative of Lederer's anemia, the etiology being undetermined, no hemolysins having been demonstrated. The presence of the megaloblasts in the bone marrow along with the diarrhea may be indicative of failure to absorb a sufficient extrinsic factor from the intestine. I believe that a rather severe infection was the cause of the anemia and that transfusions and penicillin were possibly life saving. How much the administration of liver extract contributed to the child's recovery is unknown, however, its use seems logical.

The main points in support of the diagnosis of hemolytic anemia are the anemia, spherocytosis, bilirubinemia, reticulocytosis, and hematuria. Paleness, but no clinical jaundice was evident.

Megaloblastic anemia does not have as fulminating an onset as this patient's illness had, and tends to run a more subacute or chronic course. The normal fragility of the patient's blood and lack of any demonstrable hereditary factor would appear to eliminate an acute exacerbation of chronic familial hemolytic anemia.

It is believed that the diagnosis of acute hemolytic anemia of megaloblastic type is justified. In many respects this illness was similar in its course to Lederer's anemia.

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MEASLES ENCEPHALITIS

Case Report No. 173

Harold W. Bischoff, M.D.: A. S. 49–3517

A. S., a nine year old white female was admitted to Children's Hospital on March 17, 1949 with the history of a measles rash of five days' duration and a convulsion seven hours before hospital entry.

The patient had become ill seven days prior to admission. The first manifestation of her disease was anorexia followed by pharyngitis, rhinitis, conjunctivitis, cough, and photophobia. Within forty-eight hours she had developed what was thought to be a typical morbilliform rash.

Two days before hospitalization, the child was seen by her physician who found evidence of infiltration at the base of the left lung. At that time, the temperature was 104.5 F. Therapy consisted of oral sulfadiazine and daily injections of parenteral penicillin. Twenty-four hours later the girl's temperature was normal, yet she appeared to be drowsy and refused food and fluids.

At 3:00 P.M. on the day of hospital entry there was a sudden onset of a convulsion which her physician described as being of the Jacksonian type. It involved especially the left hand and arm and cyanosis was present. This convulsive seizure was controlled by the intravenous administration of sodium pentothal. A lumbar puncture was performed and the spinal pressure was said to have been normal. The cell count was 63 cells per cubic millimeter and the Pandy test was negative. No record was obtained of the spinal fluid sugar content. Following this procedure, the patient was transferred to Children's Hospital.

The father and mother are living and well. There are two siblings, a brother aged three and one-half years and a sister aged seventeen months. At the onset of the patient's rash, the brother was given a "modifying dose" injection of immune globulin and the smaller sister was given a "preventive dose" injection of the same preparation. Further family history was negative.

In the past history, it was revealed that the child had chickenpox at three and one-half years of age, pneumonia at seven years, and mumps at eight years. A tonsillectomy and adenoidectomy were performed at four years of age. It is also of interest to note that three or four years ago the patient had what was diagnosed by a dermatologist as an "allergic" reaction to sulfa-medication applied topically.

Physical examination on admission revealed a well developed and nourished white female who was covered from head to foot with a typical

measles rash. The rash varied in intensity and color from a light pink to a dark red. The area of rash which was colored dark red was limited entirely to the lower right arm, right forearm, and hand. The child was comatose and did not respond to nocioceptive stimuli. The skin was hot and dry. The posterior cervical nodes were enlarged and there was a bilateral inguinal lymphadenopathy.

The neck showed considerable resistance to forward flexion and the back was arched. The pupils were round, regular, and equal and responded to light directly and consensually. The eyes were closed; however, when the lids were raised manually, the eyes were found to stare forward. There were occasional searching movements of the eyes but there was no nystagmus. There was a bilateral bulbar conjunctivitis. Fundoscopic examination was unsatisfactory.

Both typanic membranes were normal. The mucous membranes of the nasal passages were hyperemic but no obstruction was noted.

It was not possible to observe the throat because of a marked trismus. The mucous membranes of the cheeks were mottled and some fresh blood was noted on the left upper gum anteriorly. No teeth were missing.

The thorax was symmetrical, well-clothed and moved with respiration. No definite dullness over the lung fields was observed. However, there was bronchial breathing over the right upper chest anteriorly and some fine râles could be heard over both bases posteriorly.

The heart, blood pressure, abdomen, and genitalia were normal.

The arms were drawn up and flexed on the chest. The legs generally remained extended. There was "lead pipe" rigidity of both arms and both legs.

The deep reflexes were absent in the arms and legs bilaterally. The abdominal reflexes were absent as was the glabella reflex. Kernig and Brudzinski reflexes were both positive. There was a text-book picture of a Babinski reflex on the right, sustained patella clonus on the right, and a few clonic jerks on the left. Non-sustained ankle clonus was observed on the right but there was none on the left. When the gastrocnemius and soleus muscles were stimulated on the left in an effort to elicit clonus, they immediately went into sustained contraction pulling the foot down into the equinovarus position.

A spinal tap was performed which revealed 123 cells per cu. mm., 60 mgm. % of protein, and 40 mgm. % of sugar. A differential count of the spinal fluid cells showed 68 per cent polymorphonuclears, 30 per cent lymphocytes, and 2 per cent endothelial cells. The spinal fluid manometric pressure was 125 mm. of water. Pressure in the right jugular brought the pressure to 230 mm. of H_2O and there was no response on the left.

Innumerable gram negative bacteria were found in the smear from the

fourth tube. It should be noted that pressure had been exerted over the right jugular while the fluid in the third and fourth tubes was being collected. In spite of the fact that large numbers of organisms were seen on the smear of the first spinal fluid, there failed to be growth in the culture. Blood culture on admission was negative.

A hemogram on admission showed 12.5 grams of hemoglobin and four million red blood cells. The white blood count numbered 15,000 with a normal differential. A urinalysis done the following day was normal.

In discussing the child's condition with the mother after completion of the examination, she remarked that the right arm had not been as dark prior to the application of the tourniquet for administration of sedation earlier that day. A tourniquet was immediately applied to the left arm and within 30 seconds the rash darkened and petechiae appeared.

Smears were made from the newly appeared petechial areas and also from those on the right arm and abdomen. Microscopic examination of gram-stains of these smears revealed no organisms.

The patient was started on intramuscular aureomycin, 50 mgm. in 2 cc. of 0.5% procaine every four hours. This was continued for four days when the medicine was changed to the oral preparation, 250 mgm. every four hours, given in a menstruum of milk by gavage. The oral aureomycin was discontinued after 48 hours. Two days after admission the child was still comatose but did respond to painful stimuli. A repeat spinal tap revealed 17 cells/cu. mm. with 70% polymorphonuclears and 30% lymphocytes. Protein was 20 mgm. % and sugar 45 mgm. %. No organisms were seen on the smear and culture of the spinal fluid was negative. The second day after admission the child had a convulsion which lasted only about a minute and involved the right side of the face and the right shoulder.

On this day one examiner found that the eyes turned up and to the left. All deep tendon reflexes were hyperactive with the exception of those in the right upper extremity. The abdominal reflexes were absent and there was a bilateral positive Babinski.

The following day all deep tendon reflexes were hyperactive. The Babinskis were negative and the child was non-responsive to stimuli.

On the 21st of March, four days after admission and eight days after the appearance of the rash, the child opened her eyes and seemed to follow when she was called.

In the following six days the child improved somewhat. She was fed by gavage. On the sixth hospital day, for the first time since the onset of her disease, the girl drank a little water from a glass. On this day she was also said to have smiled. From this point onward there was slow but gradual recovery. By the time of her discharge the girl still had some difficulty in integration especially if a question were somewhat difficult. Single questions

were answered readily. She recognized everyone apparently, and her mood was appropriate at all times.

DISCUSSION

Joseph M. LoPresti, M.D.: In the past decade, encephalitis complicated the course of measles in twenty cases at this hospital, i.e., approximately 3 per cent of all the cases of measles admitted during this time. This figure does not represent the incidence of measles encephalitis, since only complicated measles are admitted here. It is rather, a reflection of the occurrence of this disease process in all of the measles complications. In such a small series no definite conclusions can be made, but certain definite trends are apparent.

An average of 8.6 days elapsed from the onset of catarrhal symptoms to the beginning of the encephalitic syndrome. Three cases occurred five days after the onset of measles, and one child developed encephalitis fourteen

CHART 1. Age, sex, and racial incidence of measles encephalitis

Age	*Number*	*Per cent*
0–1 year	0	0
2–3 years	3	15
4–5 years	5	25
6–7 years	6	30
8–9 years	6	30
Total	20	100

Male 9. Female 11.
White 19. Colored 1.

days from the onset of illness. All of these children developed encephalitis *after* the evolution of the rash. There were eleven cases who developed their symptoms during the eruptive stage of measles; the remaining nine cases were noted to evolve after the eruption had reached its height.

The age incidence is indicated in the first chart. No case was seen under the age of one year. The youngest was a twenty month old colored male. It is readily appreciated that 85 per cent of the cases in this series occurred after four years of age. The racial and sexual distribution showed an interesting trend. No predilection for either sex was noted. However, nineteen cases occurred in white children (95 per cent in this series).

The second chart demonstrates the signs and symptoms in the order of frequency with which they were noted. Fever, listlessness, lethargy, and stupor; convulsions, and coma were most frequently encountered. In four instances a major convulsive seizure was the first indication of encephalitis. It was also noted that, although it was not common in this series, urinary retention was present in two cases. The neurological examination reveals

that, by far, the most frequent finding was nuchal rigidity. This sign was absent most often in those cases where heavy sedation had been used to control convulsive seizures.

The third chart shows the average spinal fluid picture which one may expect to find in measles encephalitis. It must be pointed out that there were four cases in which the spinal fluid was normal. Two of these patients had residual findings on discharge from the hospital. One, a five year old white male, had a left-sided hemiplegia. The other, a three year old white female, was ataxic when discharged from the hospital. There was no cor-

CHART 2. Signs, symptoms, and neurologic findings in measles encephalitis

Signs and symptoms	*Per cent*
Fever	65
Listlessness, lethargy, stupor	50
Convulsions	40
Coma	30
Vomiting	25
Headache	20
Ataxia	20
Restlessness, irritability	20
Mental and speech changes	15
Urinary retention	10
Neurologic findings:	
Nuchal rigidity	70
Deep reflex changes	45
Positive Babinski	35
Positive Kernig	30
Stiff back	15
Positive Brudzinski	10

CHART 3. Average spinal fluid picture in measles encephalitis

Number of cells	*160 per cubic millimeter*
Polymorphonuclears	53%
Lymphocytes	47%
Protein	20 mgm. %
Sugar	45 mgm. %

relation between spinal fluid changes and the severity of the encephalitis. The patient with the most abnormal spinal fluid, a seven year old white male who had 770 cells per cubic millimeter, had a rather mild encephalitis and was discharged with no residuals.

Time and circumstances did not permit a thorough investigation into the progress and severity of encephalitic residua. Four children still had changes when they were discharged from the hospital. The changes included:

1. Mental alterations, e.g., regression; extreme emotional liability.
2. Hemiparesis.
3. Hemiplegia.

4. Spastic paralysis of all extremities.
5. Ataxia.
6. Incontinence.
7. Recurrent convulsive seizures.

The severest of these was a five year old white female who had only 40 cells per cubic millimeter in her spinal fluid. This child is still institutionalized. She shows extreme emotional lability, is subject to frequent major convulsive seizures, and has a right-sided hemiparesis.

Down through the years as the new therapeutic agents became the vogue, they were employed, one by one, in the treatment of measles encephalitis. None of them appeared to exert a beneficial effect on the encephalitic process. The two deaths that occurred in this series received large amounts of immune gamma globulin without apparent benefit. When respiratory complications were present, e.g., otitis media, tonsillitis, and bronchopneumonia, the sulfones, and more recently penicillin, seemed to modify the course of these complications.

There were two fatalities from measles encephalitis.

1. P. G., a six year old white male, was admitted in 1944 five days after the onset of his illness and at the height of the morbilliform eruption. His presenting symptoms were fever of 102°F., lethargy, nuchal rigidity, and hyperactive reflexes. There were also signs of bronchopneumonia. Spinal fluid examination revealed 82 cells per cubic millimeter of which 10% were polymorphonuclear and 90% were lymphocytes. The protein was 5 mgm. % and the sugar was normal. The patient received large doses of gamma globulin. In spite of all measures, there was increasing stupor, the temperature rose to 109°F., and he expired during a convulsive seizure eleven days after admission.

2. J. M., a nine year old white male was admitted in 1946, seven days after the onset of his illness and during the eruptive stage of measles. He was admitted in coma, the temperature was 102.6°F. There was nuchal rigidity, spasticity of all extremities, positive Kernig and Babinski signs. There were 310 cells per cubic millimeter in his spinal fluid with 82% polymorphonuclears and 18% lymphocytes. The protein was 25 mgm. % and the sugar 25 mgm. %. This patient also received gamma globulin. He had a stormy hospital course sparked by frequent major convulsive seizures. He finally died thirty-one days after admission during one of these convulsions.

Although this series is quite small and the hazards of making any definite statements is recognized, it is felt that the following conclusions are valid:

1. Encephalitis is not a common complication of measles.
2. Encephalitis as a complication of measles occurs most frequently in white children.
3. This complication rarely, if ever, occurs during the catarrhal stage

of measles and is very rare under the age of one year. It occurs more frequently after the age of four.

4. The most common sign of encephalitis is nuchal rigidity.
5. There seems to be no correlation between the encephalitic inflammatory reaction as reflected in the spinal fluid changes and the severity of the disease.
6. There is no specific therapy for this complication of measles.
7. Measles encephalitis is one of the most severe of all of the encephalitides; fatalities and residua are not uncommon.

DISCUSSION

William F. Burdick, M.D.: The causative agent of encephalitis complicating measles has not been established.[1] Shaffer, Rake and Hodes isolated the measles virus from the brain of a child who died of encephalitis a considerable period of time after the subsidence of the rash.[2] The possibility of the virus only being present in the contaminating blood, however, could not be eliminated.

There are three common theories of etiology: (1) The theory that the disease is actually due to the virus of measles; (2) the activation theory, that the measles virus activated another virus which is dormant in the patient; (3) the allergic theory, that the condition is due to an allergic response of the central nervous system to the virus of measles. The first theory has more adherents than the others.

The disease could better be called measles encephalomyelitis because the process may involve the spinal cord as well as the brain. However, cases in which there is clinical evidence of involvement of the cord are not common.

In a recent report by Appleton et al of a series of 74 cases with involvement of the central nervous system encephalitis, myelitis or both in association with an attack of measles, some very interesting and informative material is presented and their necropsy studies on 6 of these cases presents important changes in the pathological picture of these patients suffering from this disease.[3]

In this series of cases the ages ranged from 14 months to 35 years, thus showing that adults are no less prone to the disease than are children.

The incidence of the complication is said to be about one or slightly less in 1000 cases of measles or about 0.1 per cent.

The pathological process is diffuse and varies greatly as regards both the area involved and the intensity of the insult. The clinical course therefore is extremely variable and almost every sign and symptom indicative of involvement of the central nervous system may be encountered. The

clinical picture in the acute phase may change radically from day to day and even from hour to hour.

The encephalitis of measles is morphologically an inflammatory disease. The early lesions are lymphocytic infiltration of the walls of small veins in the gray and white matter of the brain, meningeal cellular infiltration, degeneration of ganglion cells and microglial proliferation. Perivascular loss of myelin is a later degenerative manifestation developing after three days of clinical encephalitis.

The prognosis of measles encephalitis should always be guarded. The mortality rate is between 9 and 10 per cent. About 60 per cent of the cases may have sequelae, the commonest of which are psychosis, mental retardation, paralysis and personality deviation. The 40 per cent of cases escaping without permanent sequelae may require 6 months or longer to clear up.

The treatment of these patients is entirely symptomatic and supportive. The use of gamma globulin as a therapeutic measure in these cases is thought to be of little value but has not been thoroughly evaluated. The use of aureomycin in this patient was thought to have had no bearing on the recovery.

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CLINICO-PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D.
Assisted by: William M. Crowell, M.D.
Francis J. Troendle, M.D.
By Invitation: Benjamin Manchester, M.D.

William M. Crowell, M.D. R. B. 47–8433

R. B., a thirteen day old white female was admitted to this hospital on August 15 at 2:00 P.M., and died on August 16 at 6:30 A.M.

This infant was the youngest of three and the product of a nine months' gestation and normal hospital delivery. The birth weight was eight pounds, ten and one-half ounces, and a pediatrician's examination was said to have been entirely normal. Apparently the baby did very well on breast and complimentary formula until the day before admission. The family history was entirely non-contributory and the siblings were living and well.

On the day before admission, August 14, the mother noted that the child's usual red color changed to a bluish-white and that the hands and feet were cold. These signs were present on admission together with the vomiting of feedings. The physical examination disclosed a well developed and well nourished infant (too ill to be weighed) who was propped up in an oxygen tent and showed paleness plus circumoral cyanosis. The lungs were clear; the respirations were rapid and labored; the heart questionably slightly enlarged; the heart rate was very rapid (no specific rate recorded at this time) with a regular rhythme; and the liver was palpable one finger's breadth below the right costal margin. The remainder of the physical examination was non-contributory.

It was the impression of the attending physician that this was a case of tachycardia secondary to infection; however, when penicillin was suggested, the consulting cardiologist thought that the stimulus of frequent hypodermic injections was contraindicated.

By 9:00 P.M. that evening a CO_2 combining power was 32 volumes per cent so one-sixth molar lactate was begun by clysis. By 11:30 P.M. the respirations were 90 at which time the cardiologist advised 60 cc. of sixth molar lactate to be given intravenously which was done and after this the respirations remained between 80 and 90 per minute. At 6:20 A.M. the respirations ceased while the baby was feeding.

A chest x-ray revealed the heart to be greatly enlarged to the left with particular enlargement of the left supracardiac shadow. The impression was a congenital heart, the dimensions of which were 2.3 cm. to the right and 4.9 cm. to the left. The lung parenchyma was congested and the liver was enlarged.

An electrocardiogram was reported as follows: the rhythme was that of auricular tachycardia; the rate was 260; and the P.R. Interval demonstrated the P wave not identified in any of the leads. The Q.R.S. complexes were widened, slurred, and inverted in all leads and the Q.R.S. was 0.12. There were upright T waves in all leads. The interpretation was Auricular Tachycardia with aberrant ventricular responses or Ventricular Tachycardia.

DISCUSSION

Benjamin Manchester, M.D.: The diagnosis of a cardiovascular anomaly is often easier to make from a post mortem protocol than while the infant is alive. The data submitted is limited, due to the very short life of the patient in the hospital. There are several findings that may be helpful. The first is that the child was of nine months' gestation and normal delivery. It weighed 8 pounds 10½ ounces which indicates an unusually well nourished and vigorous fourteen days infant. The weight and size of the infant is often significant. Few children with congenital heart diseases have such development. Another pertinent fact is that a pediatrician who saw the child did not feel that the cardiovascular system was abnormal. This may mean that there were no murmurs or significant arrhythmias. Very often, murmurs may be misleading. Many congenital lesions exist without any significant physical signs during the early life of the child. Occasionally, it may require observation over a period of four to six months, and even longer to determine whether heart disease is present.

The presence of shock may be due to the tachycardia that was noted. The cyanosis described is probably due more to stasis and the associated vasomotor collapse than to any cyanotic type of heart disease; moreover, cyanosis is described to be only in the peripheral circulation and not generalized. Tachycardia in a child is a much more serious problem than in an adult. It is frequently responsible for acute cardiac dilatation and congestive heart failure in infants. Some may die when the tachycardia cannot be controlled. While the lungs were clear on the initial physical examination, signs of right heart failure were present.

Laboratory data indicate that the patient was in acidosis and did not respond to an attempt to correct this electrolyte imbalance.

The chest x-ray indicates a transverse enlargement of the heart to the right as well as to the left and congestion in the pulmonary parenchyma and confirms the presence of hepatomegaly. The x-ray is not available for examination.

As a rule, the electrocardiogram is of little help in making the diagnosis of a congenital anomaly. It often contributes or lends support to a clinical examination but rarely to the nature of the congenital defect. In this instance, however, the electrocardiogram is extremely helpful. It shows a

paroxysm of auricular tachycardia, 260 per minute, and a defective intraventricular conduction. Such a rate is too rapid for a ventricular tachycardia and is in the neighborhood of 180 to 200 per minute. It seldom exceeds these limits. Moreover, ventricular tachycardia is irregular. This does not appear to be an aberrant ventricular response for the same reason that the defective intraventricular conduction is too regular and there is little variation in the character of the Q.R.S. complexes noted. This would then suggest the presence of a conduction defect in the bundle branches. It presupposes that a defect in the upper portion of the septum is present.

In summary, a normal infant, weighing 8 pounds 10½ ounces developed tachycardia, peripheral collapse and signs of congestive heart failure and expired. The physical findings indicate that this was probably a congenital anomaly of the acyanotic variety. The common ones are of the interatrial septal defect involving the septum primum and associated with it a defect of the upper portion of the intraventricular septum or the persistence of a left superior vena cava associated with an anomalous emptying of the pulmonary veins into the right auricle directly. Another possibility, the presence of Ebstein's disease, namely a displacement of the tricuspid valve and orifice and creating an anomalous large right auricle is a rare possibility. I have not seen a case, but have read about it producing a somewhat similar picture as this. As a rule, these types of congenital anomalies are compatible with long life and alone would not cause the demise of an infant. The presence of a tachycardia in association with such an anomaly may be fatal in early life.

Just a few words about the treatment of tachycardias in infants; they require immediate attention and should be regarded as cardiac emergencies. They should be digitalized promptly and every effort made to restore normal rhythm. Cedilanid is the drug of choice; it should be given intravenously. In such an emergency, the dose for this child would be 0.33 cc. of Cedilanid intravenously and 0.10 cc. repeated at six hour intervals until full digitalization is established.

Dr. Olshaker: Is Quinidine indicated in the treatment of paroxysmal auricular tachycardia?

Dr. Manchester: In this instance, quinidine is contraindicated because of the defective intraventricular conduction. In my own experience, digitalis is superior to quinidine in the cessation of a paroxysm of auricular tachycardia. There is increasing evidence in the literature that quinidine is seldom effective. In the present instance, the infant was in failure and digitalis is preferred.

Dr. Bean: What about Digitoxin?

Dr. Manchester: It is a slower acting glycoside requiring two to six hours before it is effective.

Dr. Bean: And Digoxin?

Dr. Manchester: It is a rapidly acting glycoside but is excreted equally as fast and digitalization cannot be controlled effectively because of the variability of the maintenance dose of digoxin.

Dr. Waite: Would you consider a patent ductus arteriosus?

Dr. Manchester: I did not entertain the possibility of a ductus. Such a possibility should be considered in the differential diagnosis. It may be present in the absence of a murmur and occasionally serves as a shunt from the pulmonary artery into the aorta due to a pulmonary vascular anomaly. When such a defect is present, the ductus is less likely to close after birth because it is necessary to maintain circulation. Dr. Cassidy will tell us in a few moments how far wrong our speculation has been.

PATHOLOGIC DISCUSSION

John E. Cassidy, M.D.: The most important findings at autopsy were confined to the heart. Besides these there was congestive heart failure as evidenced by pulmonary edema and congestion, plus congestion of the liver and of the spleen.

The heart was very large measuring seven by four and eight tenths centimeters and weighing fifty-three grams. The expected weight of the heart for an infant of this age is eighteen grams. The position was transverse and there was some anterior rotation giving the impression of some malposition of the great vessels. This was not so however. On opening the heart three tumor masses were found, the largest of which was in the intraventricular septum. This one measured approximately two and one-half centimeters in diameter, was firm and seemed to be fairly well encapsulated. Another nodule approximately one-half centimeter in diameter protruded from the wall of the left ventricle and another measuring one by seven-tenths by seven-tenths centimeters was located in the posterior position of the mitral valve. The consistency of all three was the same, and on section they were firm, pink in color, and had several small hemorrhagic areas scattered throughout.

Microscopic examination revealed normal areas of myocardium adjoining the tumor nodules, the masses themselves being composed of vacuolated to semi-vacuolated muscle fibers, with an apparently bizarre irregular network of cell walls. These vacuolated cells frequently contain a central portion of cytoplasm and a peripheral vacuolated area traversed by their striated strands of cytoplasm, emanating from the central mass and extending to the cell boundary. These are so-called "spider cells."

The terms used to describe this lesion are "congenital rhabdomyoma" or "localized glycogen storage disease."

This is the second such case reported at this hospital, hence one can see

the rarity of the condition. Leach[1] gives a review of the literature concerning primary tumors of the heart and reports two cases of his own. Most of these tumors are non-malignant but the figures regarding this vary somewhat. Yater[2] in his series reported 20 per cent to be cancers and Larson and Sheppard,[3] 29 per cent.

Three main types of rhabdomyoma are described: solitary, multiple, and diffuse depending on the numbers of nodules and their distribution. Ours is the multiple type.

We wish to thank Dr. Manchester for being with us and giving us this fine discussion and differential diagnosis.

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